



Early Induction of Hypothermia During Cardiac Arrest Improves Neurological Outcomes in Patients With Out-of-Hospital Cardiac Arrest Who Undergo Emergency Cardiopulmonary Bypass and Percutaneous Coronary Intervention

Ken Nagao, MD; Kimio Kikushima, MD; Kazuhiro Watanabe, MD; Eizo Tachibana, MD; Yoshiteru Tominaga, MD*; Katsushige Tada, MD*; Mitsuru Ishii, MD*; Nobutaka Chiba, MD*; Asuka Kasai, MD*; Taketomo Soga, MD*; Masakazu Matsuzaki, MD; Kei Nishikawa, MD*; Yutaka Tateda, MD*; Harumi Ikeda, MD*; Tsukasa Yagi, MD

Background: Therapeutic hypothermia for comatose survivors of out-of-hospital cardiac arrest has demonstrated neurological benefits. Although early cooling during cardiac arrest enhances efficacy in animal studies, few clinical studies are available.

Methods and Results: The 171 patients who failed to respond to conventional cardiopulmonary resuscitation were studied prospectively. Patients underwent emergency cardiopulmonary bypass (CPB) plus intra-aortic balloon pumping, with subsequent percutaneous coronary intervention (PCI) if needed. Mild hypothermia (34°C for 3 days) was induced during cardiac arrest or after return of spontaneous circulation. Of the 171 patients, 21 (12.3%) had a favorable neurological outcome at hospital discharge. An unadjusted rate of favorable outcome decreased in a stepwise fashion for increasing quartiles of collapse-to-34°C interval ($P=0.016$). An adjusted odds ratio for favorable outcome after collapse-to-CPB interval was 0.89 (95% confidence interval (CI) 0.82–0.97) and after CPB-to-34°C interval, 0.99 (95%CI 0.98–0.99) when collapse-to-34°C interval was divided into 2 components. Favorable neurological accuracy of a collapse-to-CPB interval at a cutoff of 55.5 min and CPB-to-34°C interval at a cutoff of 21.5 min was 85.4% and 89.5%, respectively.

Conclusions: Early attainment of a core temperature had neurological benefits for patients with out-of-hospital cardiac arrest who underwent CPB and PCI.

Key Words: Cardiac arrest; Cardiopulmonary bypass; Cardiopulmonary resuscitation; Extracorporeal circulation; Hypothermia

Despite decades of efforts to promote cardiopulmonary resuscitation (CPR) science and education, the neurologically intact survival rate for patients with out-of-hospital cardiac arrest remains low worldwide, averaging 6% or less.^{1,2} Prompt bystander CPR and early defibrillation can significantly increase the chance of neurologically intact survival, but standard advanced life support (ALS) measures, such as tracheal intubation and pharmacological circulatory support, have not been shown to be beneficial to neurological outcome.^{1–3} In 2 randomized clinical trials, induced

hypothermia resulted in improved neurological outcomes,^{4,5} and the 2005 CPR Guidelines recommended that unconscious adult patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest should be cooled to 32–34°C for 12–24 h when the initial rhythm was ventricular fibrillation (VF).^{1,2} However, the number of patients who may benefit from therapeutic hypothermia is limited to approximately 8% of patients with out-of-hospital cardiac arrest.^{1,4,6} In Japan, the SOS-KANTO study showed that a favorable neurological outcome at 30 days was extremely low in patients

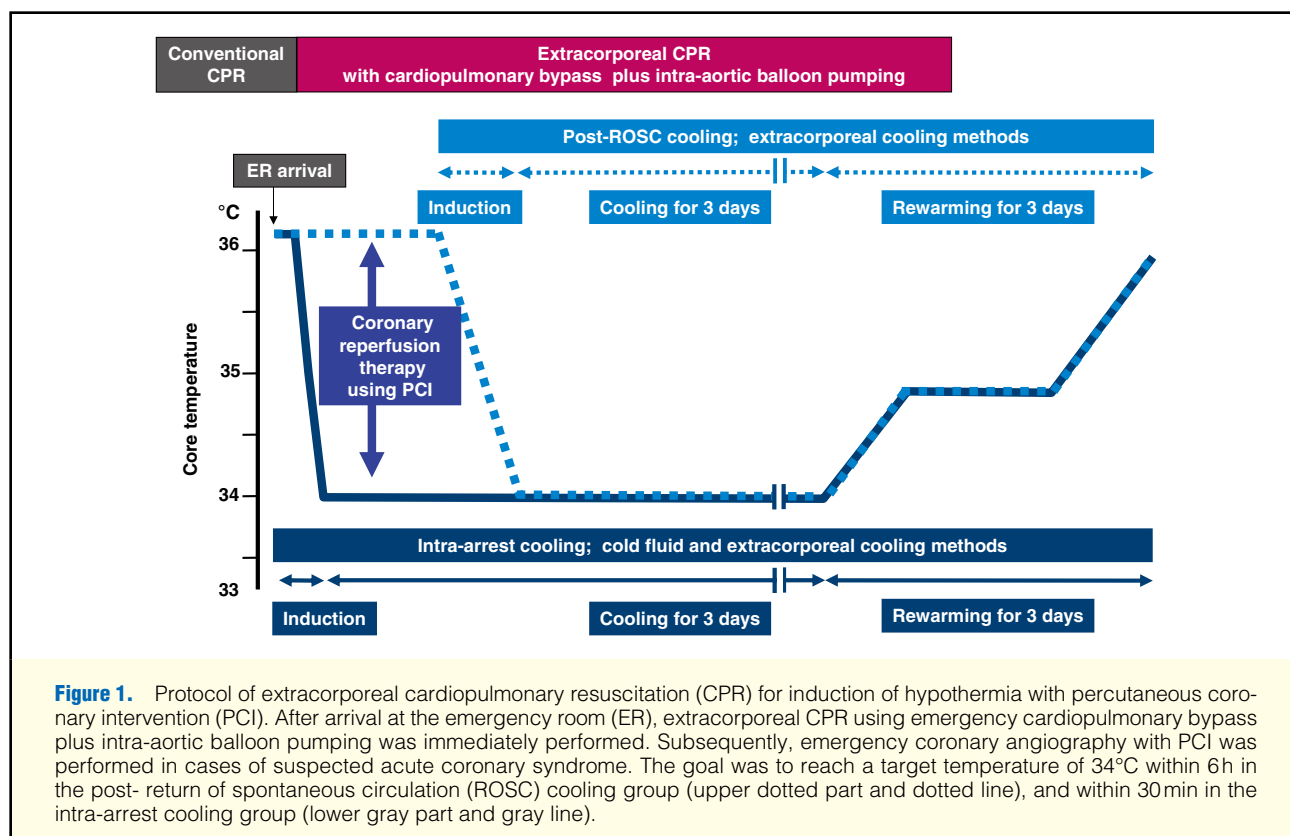
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Department of Cardiology, Resuscitation and Emergency Cardiovascular Care, *Division of Resuscitation and Emergency Cardiovascular Care, Surugadai Nihon University Hospital, Tokyo, Japan

Mailing address: Ken Nagao, MD, Department of Cardiology, Resuscitation and Emergency Cardiovascular Care, Surugadai Nihon University Hospital, 1-8-13 Kanda Surugadai, Chiyoda-ku, Tokyo 101-8309, Japan. E-mail: kennagao@med.nihon-u.ac.jp

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with out-of-hospital cardiac arrest who arrived at the emergency hospital in cardiac arrest.⁷⁻⁹

The 2005 CPR Guidelines recommended that extracorporeal CPR using emergency cardiopulmonary bypass (CPB) should be considered for patients with in-hospital cardiac arrest when the duration of the no-flow arrest was brief, and the condition leading to the cardiac arrest was reversible or amenable to heart transplantation or revascularization (Class IIb).^{1,2} Chen et al showed that emergency CPB with normothermia produced a survival benefit over conventional CPR in patients with in-hospital cardiac arrest, although they did not identify neurological benefits.¹⁰ Since 1994, we have performed extracorporeal CPR using emergency CPB plus intra-aortic balloon pumping, with subsequent percutaneous coronary intervention (PCI) if needed, on patients who arrive at the emergency room (ER) in cardiac arrest.^{11,12} Our first study showed that extracorporeal CPR with normothermia is a useful perfusion method for cardiac resuscitation, although we did not obtain satisfactory effects for cerebral resuscitation.¹¹ Our next preliminary study indicated that extracorporeal CPR for induction of hypothermia after achievement of ROSC (post-ROSC cooling) may improve the chance of a favorable neurological outcome, with a low risk of complications.¹² Recent animal studies showed that induction of hypothermia during cardiac arrest (intra-arrest cooling) provided neurological benefits.¹³⁻¹⁵ We therefore changed the timing of initiation of cooling and assessed whether early attainment of a target core temperature, inclusive of early implementation of extracorporeal CPR, had neurological benefits for patients with out-of-hospital cardiac arrest who failed to respond to conventional CPR.

Methods

Patients

We conducted a study of extracorporeal CPR for induction of hypothermia with PCI between November 2000 and December 2007 with the approval of the hospital research ethics board. Patients transported to the ER after out-of-hospital cardiac arrest were enrolled in this study when they met the following criteria: aged 18–74 years; cardiac arrest witnessed by bystanders; presumed cardiac etiology of cardiac arrest according to the Utstein style guidelines;¹⁶ estimated time interval from collapse to paramedic's arrival at patient's side within 15 min; defibrillation using automated external defibrillator by bystander and/or emergency medical personnel; and persistent cardiac arrest on arrival at the ER. Exclusion criteria were a tympanic-membrane temperature below 30°C on arrival at the ER, successful ROSC within 10 min of arrival at the ER with conventional ALS; non-cardiac etiology of cardiac arrest; or pregnancy. Patients were also excluded if their families refused to give informed consent for participation in this study.

Procedures

Our treatment protocol of extracorporeal CPR for induction of hypothermia with PCI is shown in **Figure 1**. On arrival at the ER, the attending physicians assessed as soon as possible whether a patient was eligible for this study under conventional ALS.¹⁻³ Core temperature was immediately monitored by bladder temperature until a balloon flotation right-heart catheter was placed. CPB plus intra-aortic balloon pumping was initiated when ROSC could not be achieved within 10 min of arrival. The CPB system included a centrifugal pump (Capiiox Sp pump controller, Sp-101, Terumo, Tokyo), a

hollow-fiber membrane oxygenator (Platinum cube NCVC 6000, Nipro, Osaka) and a heat exchanger unit (Heater-cooler system, MSH-15, Senko, Tokyo), and was primed with 600 ml lactated Ringer's solution with 2,000U heparin. Flow of 100% oxygen through the oxygenator was adjusted to keep PaCO₂ between 35 and 45 mmHg. The CPB flow rate was kept at $\geq 70 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ until ROSC or 3 h after commencement of CPB. After implementation of CPB plus intra-aortic balloon pumping, emergency coronary angiography was performed during cardiac arrest in cases of suspected acute coronary syndrome (ACS). Subsequently, coronary reperfusion therapy using PCI during extracorporeal CPR was performed immediately if Thrombolysis In Myocardial Infarction (TIMI) grade 0, 1, or 2 flow¹⁷ was observed in the ACS-related artery. When ROSC was achieved within 3 h of commencing CPB, the CPB flow rate was adjusted to maintain the mean arterial pressure between 90 and 120 mmHg and the pulmonary artery occlusive pressure between 15 and 20 mmHg. If hemodynamic instability persisted despite management with CPB plus intra-aortic balloon pumping, noradrenalin, dopamine, dobutamine and/or extracellular fluid infusion were administered as appropriate. Once the patient became hemodynamically stable with interruption of the CPB, CPB was weaned 24 h or more after cardiac arrest, and the intra-aortic balloon pump was removed 24 h later.

We used 2 procedures for the timing of initiation of cooling. The first method was post-ROSC cooling, used between November 2000 and November 2004. In the post-ROSC cooling group, comatose survivors who achieved ROSC within 3 h of implementing CPB were cooled to a target temperature of 34°C using the extracorporeal cooling method of CPB with a coil cooling device (KANEM or KTEK-3, as reported previously^{12,18,19}). The goal was to reach the target temperature of 34°C within 5.5 h after implementing CPB. The target temperature was then maintained for 3 days using the extracorporeal cooling method, followed by gradual rewarming over at least 3 days (warming by 0.5°C every 12 h then maintained at 35°C for 24 h). During the period of hypothermia, the patient's condition was managed as reported previously.^{12,18}

The second method was intra-arrest cooling, used between December 2004 and December 2007. In this group, patients were cooled to the target temperature of 34°C using an internal cooling method with rapid intravenous infusion of 2 L of lactated Ringer's solution at 4°C, and the extracorporeal cooling method with CPB primed with 600 ml of 4°C lactated Ringer's solution. The 500-ml bags of lactated Ringer's solution were stored in a refrigerator at 4°C before use. Until CPB implementation, 2 L of cold lactated Ringer's solution was infused using high-pressure intravenous infusion bags. The goal was to reach the target temperature of 34°C within 30 min after implementing CPB. In comatose survivors who achieved ROSC within 3 h of the implementation of CPB, the target temperature was maintained for 3 days using the extracorporeal cooling method. Management of the intra-arrest cooling group was otherwise the same for the post-ROSC cooling group.

Resuscitation attempts were documented by both paramedics and attending physicians according to the Utstein style guidelines.¹⁵ In this study coronary angiographic findings were assessed by at least 3 interventional cardiologists. Data for individual patients were entered into a database by attending physicians, and were independently cross-checked twice by different investigators. Original data were made available to the data and safety monitoring committee for independent scrutiny.

Study Endpoints

The primary endpoint was a favorable neurological outcome at hospital discharge, defined according to the Glasgow-Pittsburgh cerebral-performance category of 1 (good performance) or 2 (moderate disability) on a 5-category scale; the other categories were 3 (severe disability), 4 (a vegetative state), and 5 (death).¹⁶ The secondary endpoints were ROSC, survival for 7 days after cardiac arrest, survival to hospital discharge and a favorable neurological outcome at 1 year. ROSC was defined as palpitation of the carotid artery and the presence of systolic arterial pressure at the time of interruption of intra-aortic balloon pumping. Survival was defined as the Glasgow-Pittsburgh cerebral-performance category of 1, 2, 3, or 4.¹⁶ Neurological outcomes were defined by physicians unconnected with this study.

Statistical Analysis

Estimates of the primary endpoint, a favorable neurological outcome at hospital discharge, were 10% for the post-ROSC cooling group and 15% for the intra-arrest cooling group from analyses of our previous studies of CPB.^{12,18,19} Patients were divided into 4 groups using the quartiles of the collapse-to-34°C interval. Baseline characteristics were compared using the chi-square test for categorical variables, and the Kruskal-Wallis rank sum test for continuous variables, as appropriate. A multiple logistic regression analysis was done for independent predictors of the neurological outcome, including age, bystander CPR attempt, initial recorded cardiac arrest rhythm, and resuscitation-related time intervals. Finally we constructed a receiver-operating characteristic (ROC) curve to illustrate the various cutoff values of the collapse-to-CPB interval and the CPB-to-34°C interval as the 2 principal components of the collapse-to-34°C interval. A favorable neurological outcome was compared using the chi-square test among the 4 subsets of patients who were classified by those cutoff values. All analyses were performed using the SPSS software package (version 16.0 J SPSS; Chicago, IL, USA).

All authors had full access to the study data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

During the study period, 1,145 patients with an out-of-hospital cardiac arrest were transported to the ER. Of those, 974 patients were ineligible, so we included 171 (14.9%) patients who met the eligibility for this study: 102 had hypothermia induced after ROSC (post-ROSC cooling group), and 69 had hypothermia induced during cardiac arrest (intra-arrest cooling group).

The collapse-to-34°C interval ranged from 67 to 329 min, with a mean (\pm SD) of 204 \pm 96 min, median of 252 min, and the 25th and 75th percentile values of 94 and 286 min, respectively. Generally, the 4 groups of the patients according to the quartiles of the collapse-to-34°C interval had similar baseline characteristics, but significant differences were seen among the groups in the collapse-to-CPB interval and the CPB-to-34°C interval as principal components of the collapse-to-34°C interval (**Table**).

The primary outcome of a favorable neurological outcome at hospital discharge was seen in 21 (12.3%) of the 171 study patients. The favorable neurological outcome among all study patients decreased in stepwise fashion across the increasing quartiles of the collapse-to-34°C interval (quartile 1, 22.2% vs quartile 2, 14.6% vs quartile 3, 11.9% vs quartile 4, 0%, $P=$

Table. Baseline Characteristics of Patients According to the Quartiles of Collapse-to-34°C Interval					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value
	(<95 min)	(95–252 min)	(253–286 min)	(>286 min)	
	n=45	n=41	n=42	n=43	
Age, years	59 (53–65)	62 (50–66)	57 (52–63)	59 (54–65)	0.90
Male	41 (91%)	34 (83%)	36 (86%)	37 (86%)	0.73
Location of cardiac arrest					0.27
Home or other residence	6 (13%)	7 (17%)	6 (14%)	13 (30%)	
Public, indoors	26 (58%)	23 (56%)	20 (48%)	16 (37%)	
Public, outdoors	13 (29%)	11 (27%)	16 (38%)	14 (33%)	
First findings at arrival of paramedics					
Gasping breathing	6 (13%)	3 (7%)	5 (12%)	3 (7%)	0.68
Initial cardiac rhythm					0.49
VF/pulseless VT	34 (76%)	35 (85%)	36 (86%)	38 (88%)	
PEA	6 (13%)	5 (12%)	3 (7%)	4 (9%)	
Asystole	5 (11%)	1 (2%)	3 (7%)	1 (2%)	
Cause of cardiac arrest					0.53
Acute coronary syndrome	35 (78%)	30 (73%)	32 (76%)	34 (79%)	
Cardiomyopathy	3 (7%)	0 (0%)	2 (5%)	3 (7%)	
Others	7 (16%)	11 (27%)	8 (19%)	6 (14%)	
Medical history					
Coronary heart disease	7 (16%)	7 (17%)	7 (17%)	7 (16%)	0.99
Hypertension	10 (22%)	8 (20%)	7 (17%)	8 (19%)	0.93
Heart failure	2 (4%)	0 (0%)	0 (0%)	1 (2%)	0.35
Diabetes	5 (11%)	6 (15%)	8 (19%)	7 (16%)	0.77
Prehospital treatment					
Bystander CPR	21 (47%)	24 (59%)	26 (61%)	23 (53%)	0.51
No. of defibrillations	4 (3–5)	4 (3–5)	4 (4–5)	4 (3–4)	0.66
Time interval (min)					
From collapse to call receipt	3 (3–4)	3 (3–5)	3 (3–4)	3 (2–4)	0.64
From call receipt to patient's side	7 (6–8)	7 (6–8)	7 (6–9)	7 (6–8)	0.77
From patient's side to arrival at emergency room	23 (20–27)	23 (20–30)	23 (21–29)	24 (22–28)	0.55
From collapse to implementation of CPB	63 (58–66)	68 (60–75)	63 (59–66)	66 (63–69)	0.0001
From implementation of CPB to attainment of 34°C	24 (20–27)	32 (28–184)	214 (203–217)	240 (227–250)	<0.0001
Angiographic data of ACS					
ACS-related artery	35	30	32	34	0.82
Left main artery	0/35 (0%)	1/30 (3%)	1/32 (3%)	1/34 (3%)	
Left anterior descending artery	18/35 (51%)	16/30 (53%)	18/32 (56%)	22/34 (65%)	
Left circumflex artery	5/35 (14%)	3/30 (10%)	6/32 (19%)	5/34 (15%)	
Right coronary artery	12/35 (34%)	10/30 (33%)	7/32 (22%)	8/34 (18%)	
TIMI flow grade of ACS-related artery					
Initial angiography; 0 or 1/2/3	28/3/4	23/6/1	22/4/6	28/3/3	0.40
TIMI flow grade 3 after PCI	27/31 (87%)	26/29 (90%)	21/26 (81%)	29/31 (94%)	0.68

Data are median (Interquartile range) or number (%). Calculations based on available data. The intra-arrest cooling accounted for 100% (45/45) of the Quartile 1 group and 58% (24/41) of the Quartile 2 group.

VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; CPB, cardiopulmonary bypass; ACS, acute coronary syndrome; TIMI, Thrombolysis In Myocardial Infarction; PCI, percutaneous coronary intervention.

0.016). This association remained significant among the subgroups of patients with bystander CPR attempt, VF/pulseless ventricular tachycardia as the initial cardiac rhythm, cardiac arrest because of ACS, and TIMI flow grade 3 after PCI ($P<0.05$, respectively) (Figure 2). The secondary endpoints of survival at 7 days after cardiac arrest, survival to hospital discharge, and a favorable neurological outcome at 1 year also decreased in stepwise fashion across the increasing quartiles of the collapse-to-34°C interval ($P<0.05$, respectively), although the 4 groups had a similar secondary endpoint of ROSC (Figure 3). In addition, no significant difference was seen among the 4 groups in the collapse-to-ROSC interval

(median; quartile 1, 93 min vs quartile 2, 96 min vs quartile 3, 93 min vs quartile 4, 94 min, $P=0.146$).

A multiple logistic regression analysis for a favorable neurological outcome at hospital discharge showed that the collapse-to-34°C interval was an independent predictor, with an adjusted odds ratio (OR) of 0.99 (95% confidence interval (CI) 0.98–1.00, $P=0.035$). Another independent predictor was bystander CPR attempt (Figure 4a). When the collapse-to-CPB interval and the CPB-to-34°C interval as principal components of the collapse-to-34°C interval were entered into the model, both intervals were independent predictors of a favorable neurological outcome; an adjusted OR after

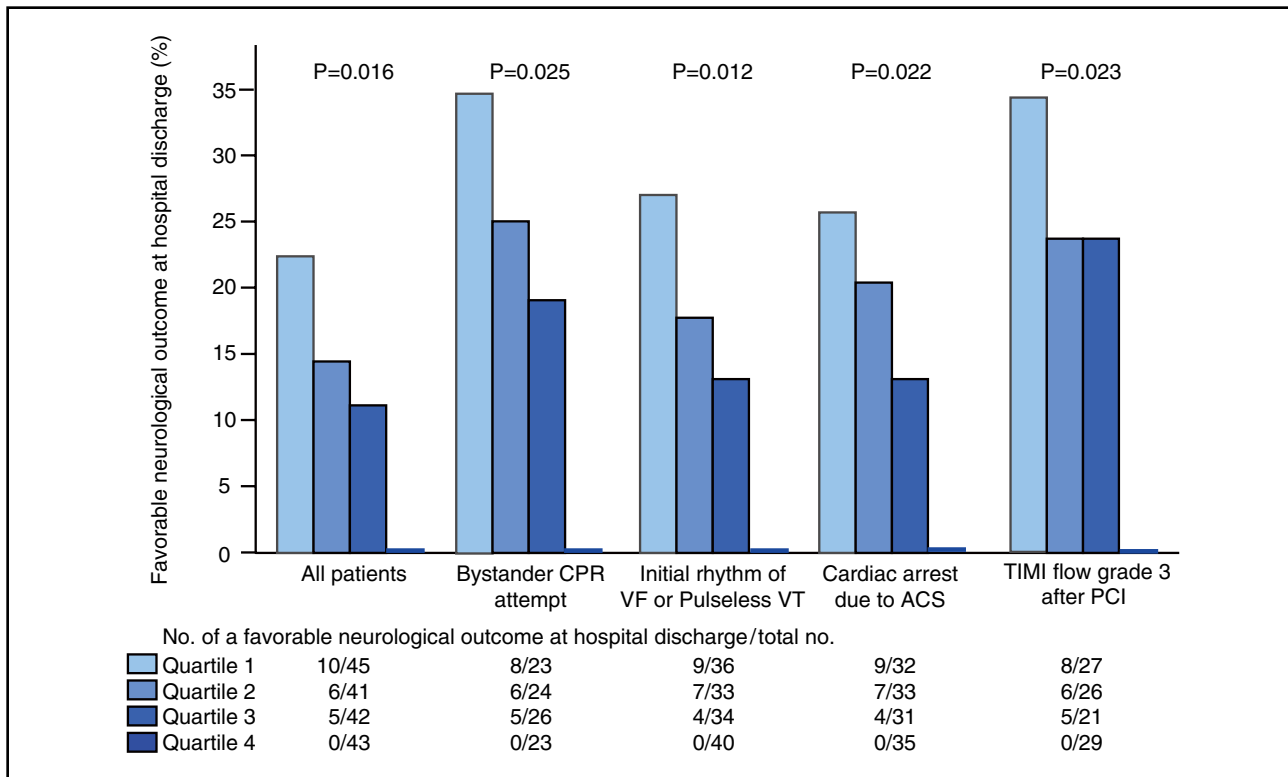


Figure 2. Association between the quartiles of the collapse-to-34°C interval and the frequency of a favorable neurological outcome at hospital discharge (primary endpoint) in all study patients and in selected subgroups. ACS, acute coronary syndrome; CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

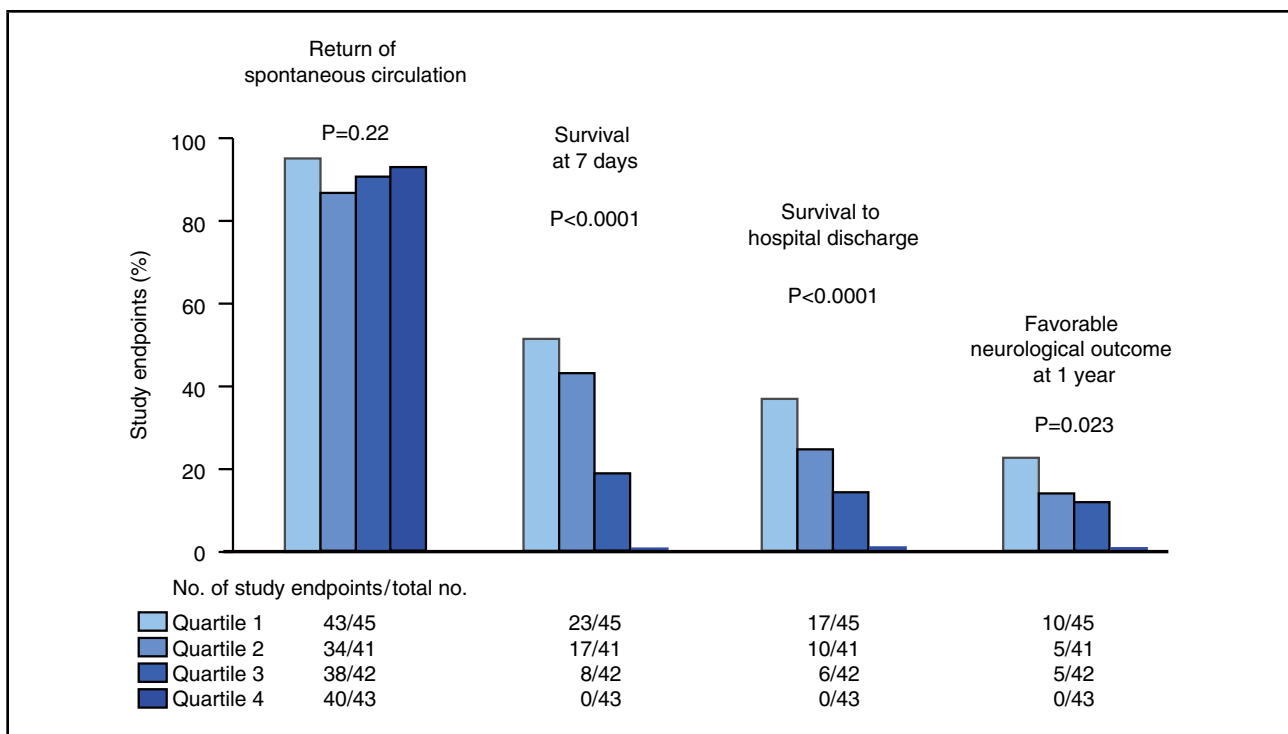
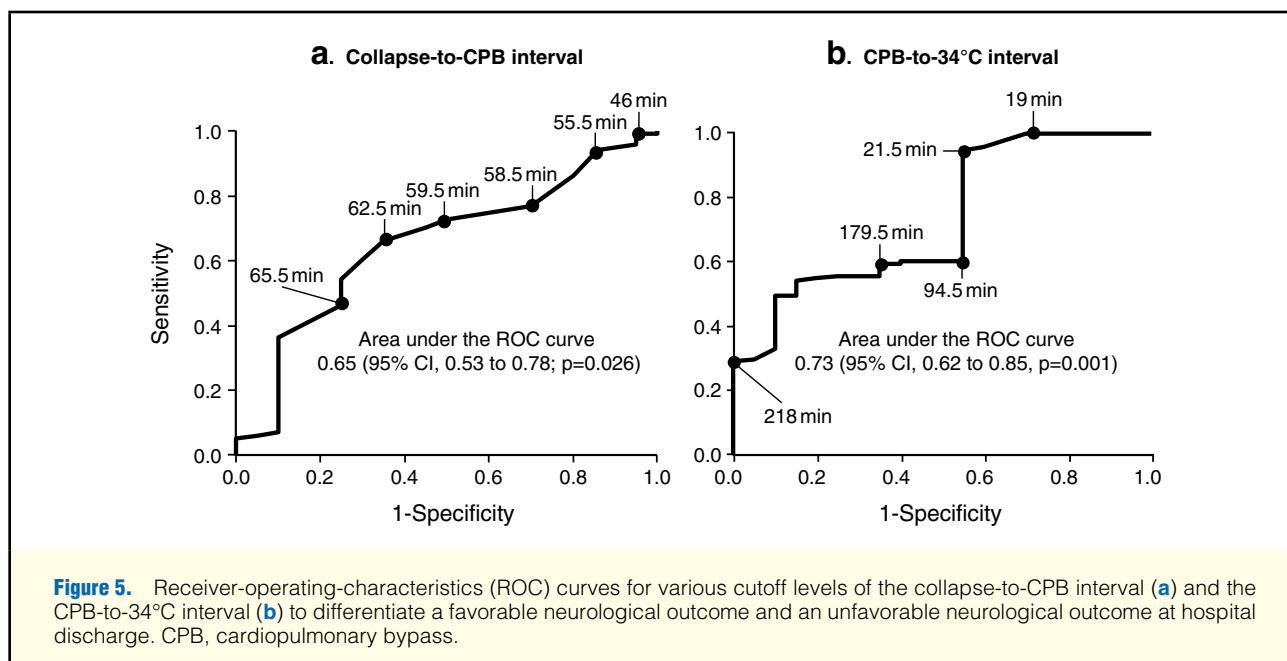
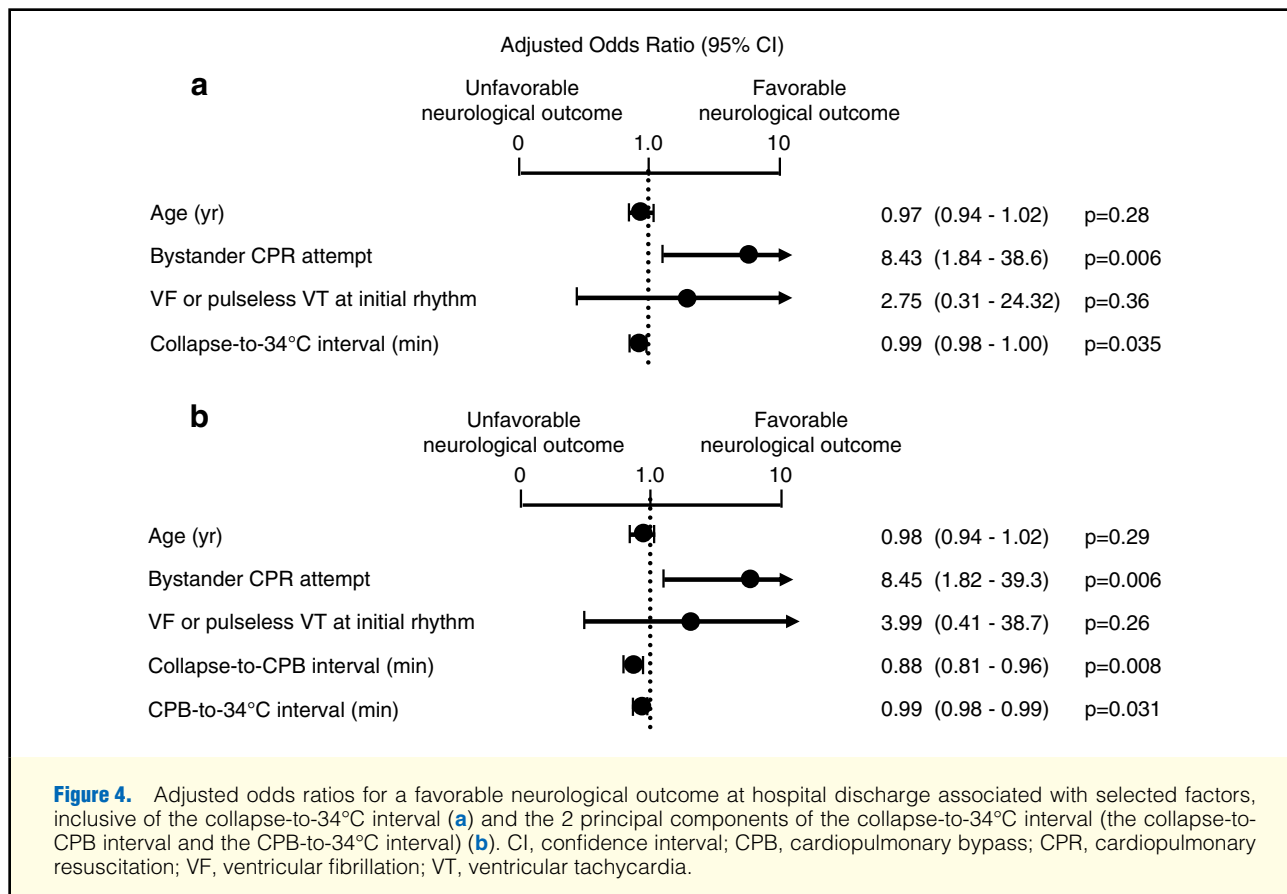
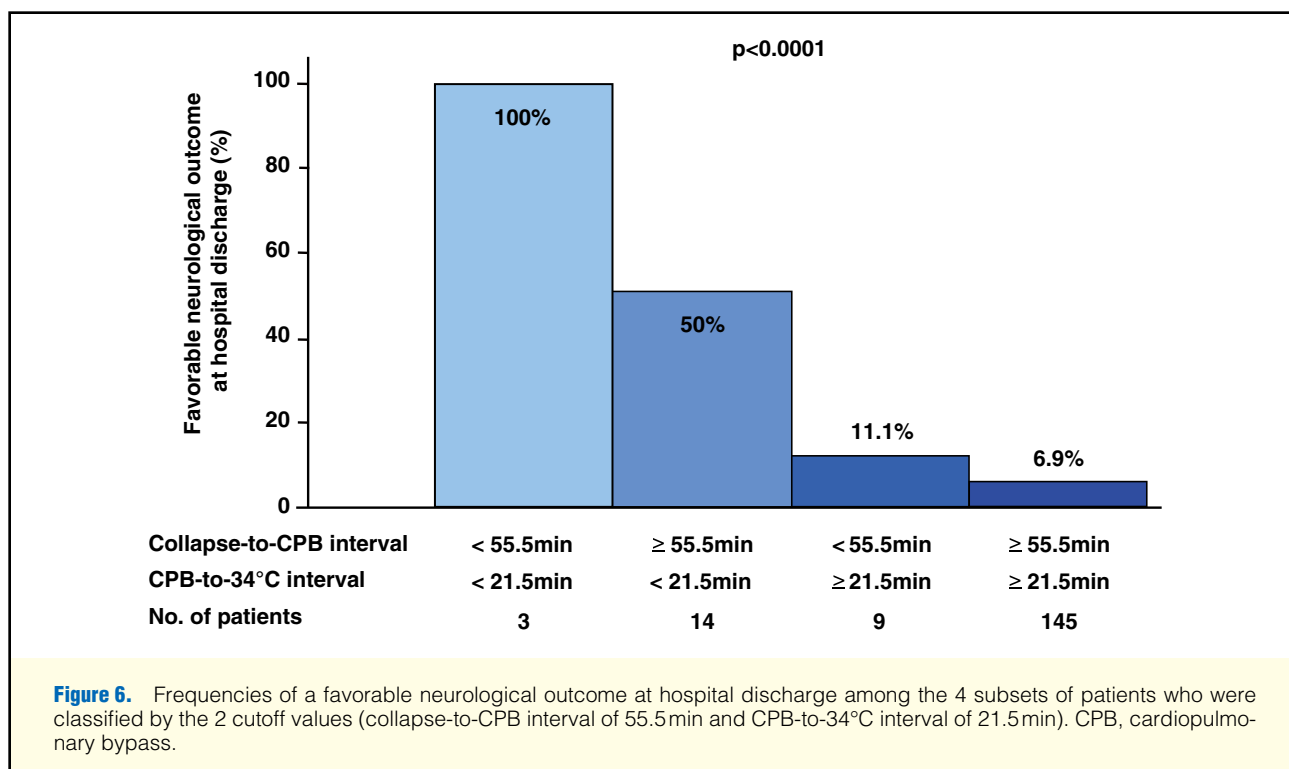


Figure 3. Association between the quartiles of the collapse-to-34°C interval and the frequencies of the secondary endpoints in all study patients.



the collapse-to-CPB interval was 0.88 (95%CI 0.81–0.96) and after the CPB-to-34°C interval, 0.99 (95%CI 0.98–0.99) (**Figure 4b**). In the subgroup of patients with ACS, the results did not change when coronary angiography findings were included in the multiple logistic-regression analyses.

The area under the ROC curve of the collapse-to-CPB interval was 0.65 (95%CI 0.53–0.78; P=0.026), and the collapse-to-CPB interval cutoff value of 55.5 min had the highest combined sensitivity and specificity, with an accuracy of 85.4% for identification of a favorable neurological



outcome. The area under the ROC curve of the CPB-to-34°C interval was 0.73 (95%CI 0.62–0.85, $P=0.001$), and the CPB-to-34°C interval cutoff value of 21.5 min had the highest combined sensitivity and specificity, with an accuracy of 89.5% (Figure 5). A significant difference was seen in the favorable neurological outcome among the 4 subsets of patients who were classified according to these cutoff values ($P=0.0001$) (Figure 6).

Discussion

This study shows that early attainment of a core temperature of 34°C during extracorporeal CPR with PCI has neurological benefits for patients with out-of-hospital cardiac arrest who fail to respond to conventional CPR. The unadjusted rate of a favorable neurological outcome at hospital discharge decreased in a stepwise fashion with the increasing quartiles of the collapse-to-34°C interval and this association remained significant in subgroups of patients (Figure 2). A multiple logistic regression analysis demonstrated that each collapse-to-CPB interval and CPB-to-34°C interval as principal components of the collapse-to-34°C interval was an independent predictor for a favorable neurological outcome at hospital discharge (Figure 4b). Each cutoff value for identification of a favorable neurological outcome was 55.5 min in the collapse-to-CPB interval and 21.5 min in the CPB-to-34°C interval (Figure 5). A significant difference was seen in the favorable neurological outcome among the 4 subsets of patients who were classified by those cutoff values (Figure 6).

Although several clinical studies of emergency CPB with normothermia for patients with cardiac arrest have been conducted,^{11,20–25} there have been few clinical studies of emergency CPB for induction of hypothermia.¹² Martin et al,²⁰ Younger et al²¹ and our previous study¹¹ showed no benefit of emergency CPB with normothermia for neurological out-

comes in patients who arrived at the ER in cardiac arrest, with the exception of cardiac arrest associated with accidental hypothermia or drug intoxication. On the other hand, Chen et al,²² Hase et al,²³ and Kano et al²⁴ found that early implementation of emergency CPB with normothermia (<45 min²³ or <60 min^{22,24} after cardiac arrest) was associated with better neurological outcomes. In this study, we showed that the optimal cutoff point for the collapse-to-CPB interval regarding a favorable neurological outcome at hospital discharge is 55.5 min. However, we consider it a most difficult task to implement CPB within 55.5 min after out-of-hospital cardiac arrest, because the recorded collapse-to-CPB intervals ranged from 47 to 94 min, with a mean (\pm SD) of 64.4 \pm 6.7 min and a median (interquartile range) of 65 (60–68) min. Such results suggest that extracorporeal CPR strategies will need to include some additional treatment for patients undergoing prolonged conventional CPR. Our preliminary study raised the possibility that extracorporeal CPR for induction of hypothermia after ROSC (post-ROSC cooling) might improve neurological outcomes.¹² Recent animal studies showed that induction of hypothermia during cardiac arrest (intra-arrest cooling) enhanced the neurological benefits, and the sooner cooling was initiated in cardiac arrest, the better the outcome.^{13–15} Using a mouse model of VF cardiac arrest (no-flow) for 8 min, Abella et al showed that early induction of intra-arrest cooling after 8 min of VF significantly increased the 72-h survival rate compared with either delayed induction of post-ROSC cooling after 30 min of VF or normothermic resuscitation.¹³ Using a canine model of VF cardiac arrest (no-flow) for 3 min, followed by 7 min of CPR, and 30 min of ALS, Nozari et al showed that induction of intra-arrest cooling after 20 min of VF significantly increased the 96-h intact survival rate compared with normothermic resuscitation. Moreover, they showed that early induction of intra-arrest cooling after 10 min of VF significantly increased the 96-h intact survival

rate compared with delayed induction of intra-arrest cooling after 20 min of VF.^{14,15} Although these results indicate that induction of intra-arrest cooling should begin within 20 min of cardiac arrest, we consider that there are substantial differences between the animal and the clinical studies in the time interval from induction of cooling to attainment of the target core temperature. In the animal studies, the target temperature was attained within 10 min after initiation of cooling using either an external or internal cooling method,^{13–15} whereas the clinical studies of therapeutic hypothermia have shown that external cooling methods require several hours to attain the target temperature, and that rapid infusion of cold fluids (30 ml/kg or 2 L) significantly reduces the core temperature, although in those particular cases the target temperature of 33–34°C was not reached.^{26–29}

Although mild hypothermia reduces the cerebral metabolic rate of oxygen consumption, and is thought to suppress many of the chemical reactions associated with reperfusion injury, the adverse effects include coagulopathy, cardiac dysrhythmias, impaired cardiac function, and increased susceptibility to infection. The prevalence and severity of these adverse effects is proportional to the depth and duration of cooling.^{1,2,6,29} Animal studies of intra-arrest cooling have shown that a target temperature $\leq 34^\circ\text{C}$ and cooling duration ≤ 12 h produces better outcomes than normothermic resuscitation (30°C for 1 h in Abella's study,¹³ 27°C or 34°C for 12 h in Nozari's studies^{14,15}). Using a porcine model of VF cardiac arrest (no-flow) of 8 min, Boddicker et al showed that pre-existing hypothermia of 30°C or 33°C facilitated significantly improved resuscitation outcomes in comparison with normothermic resuscitation, but that a temperature of 35°C was not beneficial to the resuscitation outcome.³⁰ Wu et al showed that profound hypothermia (10–15°C for 1 h), followed by mild hypothermia (34°C for 36 h) produced a better intact survival rate than normothermic resuscitation or profound hypothermia (10–15°C for 1 h), followed by mild hypothermia (34°C for 12 h) in a canine model of hemorrhagic cardiac arrest.³¹ Gunn et al reported that delayed onset brain edema following 30 min of cerebral ischemia was abolished by prolonged (3-day) hypothermia.³² In the present study, mild hypothermia (34°C) was maintained for 3 days because we considered that the patients who arrived at the ER in cardiac arrest after out-of-hospital cardiac arrest presented with more severe conditions for resuscitation than those who achieved ROSC before arrival at the ER.

In this study, the majority of patients who achieved ROSC by extracorporeal CPR died of myocardial dysfunction during the cooling stage, which suggests that cardiac function during the cooling stage after ROSC was worse in this study than in the animal studies. Several reasons might account for the low neurologically intact survival rate. There was a significant difference in the cause of the cardiac arrest between this study and the animal studies. In this study, ACS accounted for approximately 80% of cases of cardiac arrest, although coronary reperfusion therapy using PCI during cardiac arrest successfully restored antegrade coronary flow (TIMI flow grade 3) in 88% of the patients and the unadjusted rate of a favorable neurological outcome at hospital discharge decreased in a stepwise fashion with the increasing quartiles of the collapse-to-34°C interval in the subgroup of patients who achieved TIMI flow grade 3 after PCI. Knafelj et al reported that early PCI with mild hypothermia was superior to early PCI without hypothermia in comatose survivors after cardiac arrest because of ST-elevation myocardial infarction, in terms of survival benefit.³³ These findings suggest that

early induction of hypothermia and PCI protects myocardium from post-cardiac arrest syndrome in patients with out-of-hospital cardiac arrest because of ACS. It is possible that the core temperature of 34°C and/or the cooling duration of 3 days used in the present study do not represent optimum hypothermia. Further clinical studies are needed to determine the optimum target temperature and cooling duration for patients who arrive at the ER in cardiac arrest, and who are treated with extracorporeal CPR for induction of hypothermia and PCI. An ethical issue of this study was withdrawal of CPB, which is an emotionally complex decision for family and staff. We considered the following 4 factors to be associated with an irreparable state: asystole, apnea, absence of papillary response to light and papillary dilatation. When those factors continued for 3 h after commencement of CPB or appeared as a result of aggravation after admission to hospital, we asked the family for informed consent to withdrawal of CPB. Most of families agreed, but it took almost 3 days after commencement of CPB.

Study Limitations

This was neither a randomized controlled trial nor a multicenter study. Although it is difficult to conduct a randomized controlled trial of extracorporeal CPR for patients with out-of-hospital cardiac arrest in Japan, we have begun a multicenter observational study of extracorporeal CPR with hypothermia (UMIN000001403).³⁴

This study period extended past the limit of the 2005 CPR Guidelines; however, we considered this had no serious effects on the study patients who failed to respond to conventional CPR. The use of extracorporeal CPR was limited to the hospital setting and was too invasive for use in most hospitals, but the SOS-KANTO study has shown that the neurological intact survival rate is extremely low in patients with witnessed out-of-hospital cardiac arrest who arrive at hospital in cardiac arrest.^{7,8} Each year, out-of-hospital cardiac arrest occurs in approximately 100,000 people in Japan,³⁵ approximately 5,000 of whom would meet our criteria for extracorporeal CPR for induction of hypothermia. Finally, cooling was initiated after arrival at the ER, but if intravenous infusion of large-volume, ice-cold fluids was used for the pre-hospital induction of intra-arrest cooling, a favorable neurological outcome might ensue.

Conclusions

Early attainment of a core temperature of 34°C during cardiac arrest had neurological benefits for patients with out-of-hospital cardiac arrest who underwent CPB and PCI.

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Disclosures

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